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RADIOACTIVE IODINE AS AN INDICATOR IN THYROID PHYSIOLOGY

IODINE COLLECTION BY NORMAL AND HYPERPLASTIC THYROIDS IN RABBITS[1]

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In previous papers (1, 2) we have described the techniques and advantages of the use of radioactive isotopes of iodine as indicators in the study of iodine distribution and have reported preliminary results obtained with this method. This paper is concerned with the detailed results of extended experiments on normal rabbits and on rabbits which had received previous treatment designed to influence the physiologic state of the thyroid.

The majority of the experiments were conducted with the use of the radioactive isotope of iodine of mass 128, which has a half period of 25 minutes. We have also used a few samples of radioactive iodine with the half periods of 12.5 hours, 8 days and 13 days (mass numbers 130, 131 and 126 respectively) (3).

Purpose of experiments. It was the purpose of these experiments to investigate the collection of iodine by normal and hyperplastic thyroid glands, in order to establish the normal and pathological behavior toward iodine under various circumstances, and in order to determine the conditions under which it might be possible to use radioactive iodine to administer internal irradiation of the thyroid. The experiments have therefore been concerned with the measurement of the percentage collection of known doses of labelled iodine by the thyroid, as a function of time of collection, quantity of iodine injected, previous history of iodine treatment, thyrotropic hormone administration, cyanide injection, cabbage diet, sex, pregnancy, and certain combinations of these factors.

PROCEDURES. The iodine was usually administered intravenously in the form of sodium iodide obtained by dissolving labelled silver iodide in sodium thiosulphate (2). In a few experiments in which long collection times were possible because of the availability of long-period iodine iso-

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topes, subcutaneous injections were made. Animals were sacrificed by etherization, since the available radioactivities necessitated the removal of the thyroid for measurements.

The dosages of iodine administered (except in some preliminary work) were adjusted to be proportional to the weight of the animal, 2 kgm. being taken as a standard. Dosages below 0.5 mgm. were not so adjusted, however, it being of interest to determine the collection of the smallest available quantities of iodine. The range of dosages used was from less than 0.1 mgm. to 100 mgm.

In the present experiments, in addition to the information given by the gross appearance of the gland, we have used as a rough measure of the physiologic state of the thyroid the relative weight of the thyroid as compared with the body weight. It is well known that this is by no means a completely satisfactory indication of the physiologic state of the gland, but nevertheless, with a standard stimulus and large numbers of animals, it was possible to obtain statistically significant results.

For these purposes we have defined a quantity we call the thyroid index, as follows:

$$\text{Thyroid index (T.I.)} = \frac{\text{Weight of thyroid in milligrams}}{\text{Body weight in kilograms, } \times 10}$$

where the factor of 10 is introduced to give a convenient numerical result. For the normal animals in our colonies, the thyroid index of almost all animals ranged between 5.5 and 8.0. (See fig. 1.) In hyperplastic animals the index ordinarily ranges between 8.0 and 15.0, the highest value observed in our colony being 33.5 for an animal on an exclusive cabbage diet for 2 months.

In measuring thyroid iodine collection, we have introduced a quantity we call the thyroid concentration coefficient, in order to take into account the variation of size of thyroid glands among animals of the same weight. This quantity is defined by the relation

$$\text{Thyroid concentration coefficient (T.C.C.)} = \frac{\text{Thyroid iodine collection in per cent, } \times 1000}{\text{Thyroid index}}$$

The introduction of the factor 1000 has the result of making this quantity represent the concentration of iodine in the thyroid divided by the concentration in an equal weight of body tissue, assuming uniform distribution of the iodine. (Thus it is a measure of the affinity of the thyroid for iodine.)

This method of expressing the iodine collected by the thyroid is particularly useful because it gives directly the concentrating power of the

thyroid as compared with the rest of the body. In some preliminary work to determine the approximate character of the iodine collection of various stimulated glands, no indices were constructed, and the data are accordingly presented in terms of percentage. A direct comparison between percentage collection and thyroid concentration coefficient may be obtained from figures 4 and 6. Previously published data (1) have shown that the collection of iodine by the thyroid is much greater than by other organs.

All animals (except those on a cabbage diet) were maintained on a uniform rabbit chow diet, in a room kept free of any gross contamination with iodine. Thyrotropic hormone, cyanide and iodine other than the

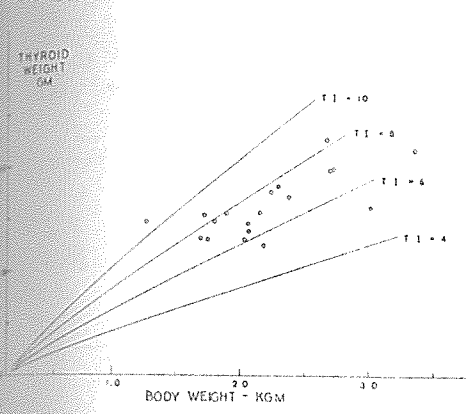

Fig. 1

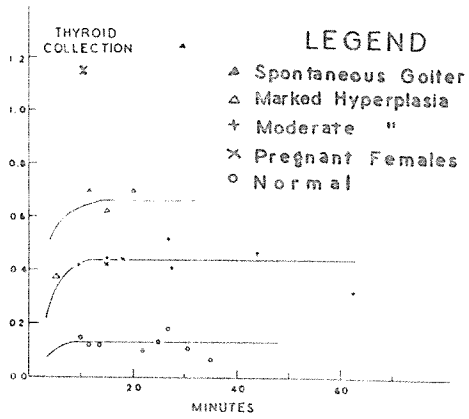

Fig. 2

Fig. 1. The variation of thyroid weight with body weight for some of the normal animals used. The radial lines are lines of constant thyroid index.

Fig. 2. Preliminary survey of the percentage collection of the thyroid in various time intervals after injection of a 10 mgm. dose of iodine. The data show the marked dependence upon the functional state of the thyroid. No precautions were taken to adjust the size of injection to the size of the animal, and the degree of hyperplasia was judged from the appearance of the gland alone.

labelled iodine were injected subcutaneously or intramuscularly. Animals on a cabbage diet were fed exclusively on cabbage, no water being given.

Cyanide-injected animals were maintained on a normal diet, and were given daily injections of 0.1 cc. of methyl cyanide daily for 2 to 4 weeks. Animals that were given 0.25 cc. daily exhibited a very high mortality rate without a great change in thyroid response.

Several different preparations of thyrotropic hormone have been used during the course of the experiments. These include suspensions of fresh beef anterior pituitary, of desiccated anterior pituitary powder supplied by Armour and Co., material prepared according to the technique of

Lambie and Trikojus (4) (in both the soluble and insoluble forms), and a thyrotropic extract prepared and kindly furnished to us by Dr. Oliver Kamm of Parke, Davis and Company. Of all these the last named was found to be the most active and satisfactory preparation. With this material 50 to 100 per cent increase of thyroid size in normal adult male rabbits may be obtained with 2 successive daily injections, corresponding to a nominal daily dose of 25 guinea-pig units. In early experiments, Ayerst, McKenna and Harrison thyrotropic preparations were used, but were found to be inactive in male rabbits, in dosages up to 10 cc.

Pretreatment with iodine. A series of experiments were undertaken to determine the effect upon the collection of a labelled dose of iodine of

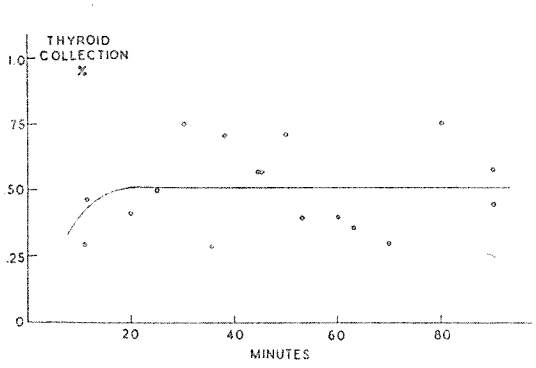

Fig. 3

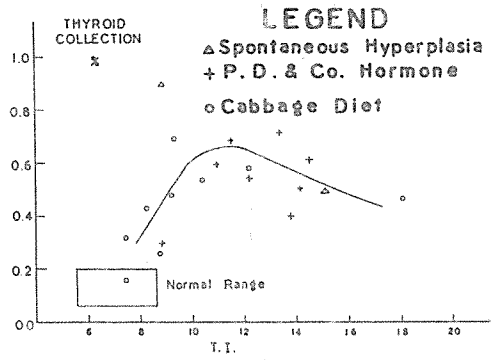

Fig. 4

Fig. 3. Percentage collection of the thyroid of normal males of injections of between 0.1 and 0.4 mgm. of iodine. No increase of collection over that of the first 10 minutes is observed for intervals up to an hour and a half.

Fig. 4. Percentage collection of hyperplastic thyroid glands of male animals. Hyperplasia induced by cabbage diet, by injection with Parke, Davis and Company thyrotropic hormone, and of spontaneous occurrence. Injection 5 mgm. per standard 2 kgm. animal. Collection time 15 minutes. The differently treated animals show experimentally indistinguishable responses, with a maximum collection at T. I. ca. 11 or 12. These animals are referred to as type 1.

previous iodine treatment. In these experiments the labelled dose of iodine was always 5 mgm., while the amount used in pretreatment was varied from 5 mgm. to 100. The time elapsing between pretreatment and injection of the labelled dose of iodine was varied from several minutes to several days.

Experiments with more than one radioactive isotope. In some of these experiments it was possible to label the dose used for pretreatment as well as the succeeding dose, using a different radioactive isotope for each dose, and distinguishing between the 2 or more radioactivities found in the thyroid by following the decay curve of the total radioactivity in the

gland, and analyzing it into its several components. In the analogy of labelling, this corresponds to the use of labels of different colors for the different doses.

RESULTS. Most of our data are presented in graphical form, in figures 1 to 10.

Using the long-period isotopes referred to above, we have obtained some data on the collection of single doses of iodine in hyperplastic thyroids in periods up to 8 days. The results show that the collection in type 1 animals (see figs. 4-6 for explanation of different types) tends to increase until the total collection has reached the value of about 40 to 50 micrograms, and then does not increase further. The length of time this takes

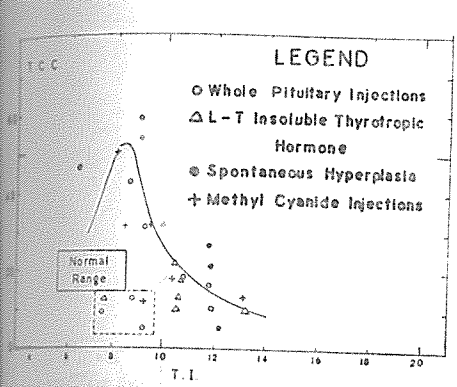

Fig. 5

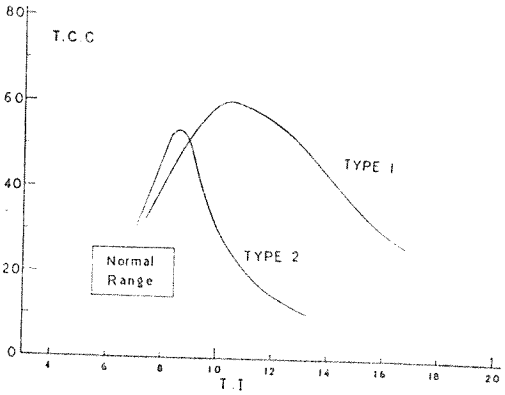

Fig. 6

Fig. 5. Thyroid collection coefficients of male animals treated as follows: saline suspensions of fresh beef anterior pituitary, insoluble thyrotropic hormone prepared according to the method of Lambie and Trikojus, methyl cyanide injected, and untreated animals with spontaneous hyperplasia. Injection 5 mgm. per standard 2-kgm. animal. Collection time 15 minutes. For a discussion of the points in the dotted rectangle, which were not taken into account in drawing the curve, see the section entitled "Discussion." These animals are referred to as type 2.

Fig. 6. Thyroid concentration coefficients for the data of figures 4 and 5.

depends mainly upon the total quantity of iodine injected. From figure 9 this may occur in as little as 15 minutes. The smallest quantities of long-period labelled iodine injected have been of the order of 1.0 to 1.5 mgm. The thyroid collection of this quantity may go as high as 6 per cent within a day, in animals on a cabbage diet. This is to be compared with collections of as much as 6 per cent within 15 minutes with injections of ca. 0.2 mgm.

In an extension of the results given in figure 10, 6 animals have been injected with 2 successive labelled doses of iodine and the collection from each dose measured. The results seem to show that if a moderately large collection occurs from the first dose, the collection of the second dose is

inhibited. Thus an animal which in 19 hours collected 53 micrograms from a 4 mgm. injection collected less than 4 micrograms from the subsequent 5 mgm. injection. On the other hand, an animal which had collected only 20 micrograms from a 5.5 mgm. injection in 31 hours, collected 7 micrograms from the subsequent 5 mgm. injection. The collection time of the second injection was always 15 minutes. In one animal whose collection time was 8 days, the collection was not much more than it would have been in 15 minutes.

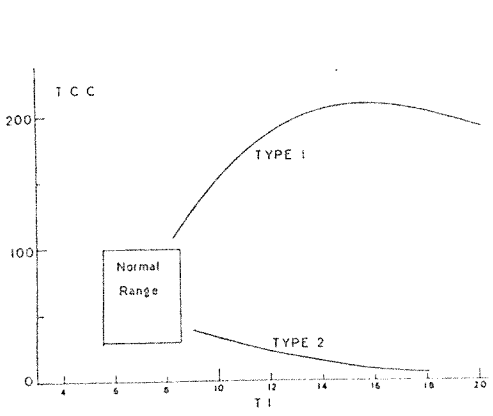

Fig. 7

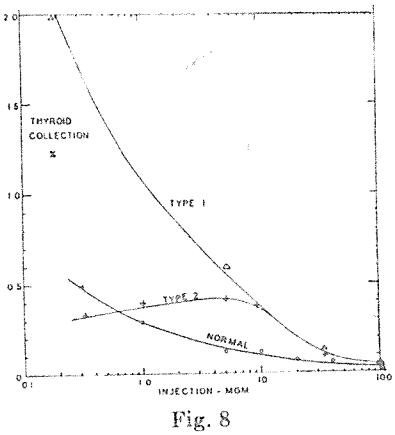

Fig. 8

Fig. 7. Same type of data as figure 6 for injections of 0.2 to 0.5 mgm. per standard 2-kgm. animal. In type 2 animals are now included some which received a dilute acetic acid suspension of Armour's desiccated pituitary tablets, and some receiving the soluble thyrotropic hormone prepared according to the method of Lambie and Trikojus (4). The curve for type 1 animals is only approximate in character, since the scattering of the values of the thyroid collection coefficient is great, the values ranging from 100 to 500. The number of animals used was 12 type 1, 20 type 2.

Fig. 8. Variation of the percentage iodine collection of the thyroid in 15 minutes with the quantity of iodine injected. The curves for hyperplastic animals are for average thyroid index 10. Total number of animals used: 39 type 1, 68 type 2, 69 normal.

In most of the experiments on pretreatment with iodine, the premedication was accomplished with ordinary iodine. The effects of premedication depend upon a large number of other factors in animals with hyperplastic thyroids. The subsequent collection appears to depend not only upon the quantity of the premedicating dose, but also upon the thyroid index of the animals, the type of thyroid stimulation, and to some extent the time elapsing between the premedicating dose and the labelled dose. In normal animals a dose of about 50 mgm. is necessary to reduce the collection of the labelled dose to half the value expected of a normal untreated animal. In the case of type 1 animals, only 8 mgm. will do the same within 4 to 6 hours. (See fig. 10.)